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AMINOACIDS IN THE COURSE OF TOXICO-ALLERGIC DERMATITIS

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Abstract

The study aimed at identifying patterns of protein metabolism changes during toxico-allergic dermatoses for the correct choice of tactics for therapeutic interventions.

In order to identify patterns the characteristics of amino acid composition of the serum of patients with polymorphic exudative erythema, patients with Stevens-Johnson syndrome and patients with toxic epidermal necrolysis were studied.

Reduced amino acid content, involved in the synthesis of glutathione in the tissues (glycine, cysteine and glutamic acid) and increased arginine content (antioxidant nitrogen) were noted in blood. Changes in the content of other amino acids and amines (methionine, proline, ornithine, taurine) are associated with them metabolically. Toxico-allergic dermatoses are accompanied by significant changes in the blood parameters of the protein metabolism.

Disaminoacidemia in case of multiform exudative erythema is a consequence of the activation of lipid peroxidation and weakening of the body antioxidant defenses. Hypoaminoacidemia in Stevens-Johnson syndrome and in the initial phase of toxico-allergic dermatitis can be caused by the violation of protein synthesis, increased permeability of blood vessels and release of proteins from the vascular bed. In the conditions of hypoxia the possibility of slowing down the speed of digestion of proteins to amino acids is not excluded. Reducing the level of free amino acids in blood in Stevens-Johnson syndrome and toxico-allergic dermatoses (in the initial period) is the result of intensive use of free amino acids for the synthesis of protein molecules as a result of skin lesion. The severity and nature of metabolic disorders determine the features of the content of free amino acids and their metabolites in patients.

Keywords: *multiform exudative erythema, Stevens-Johnson syndrome, Lyell's syndrome, amino acid imbalance and disorders of protein metabolism in toxico-allergic dermatoses.*

Introduction

Rare but life threatening collateral skin reactions such as Stevens-Johnson syndrome and toxic epidermal necrolysis are the subject of multiple investigations. Authors point to heavy necrosis and epidermis sublation, as well as difference in etiology. Statistic shows that drug-induced reactions are the most common (90% cases), and genetic factors are prevailing. Clinical immunological and therapeutic peculiarities of erythema multiforme, as well as drug implementation experience for its precaution is widely discussed in literature [*Saurat J, 1999; Ivanov O, 2003; Khaldina M et al., 2005; Rizhko P et al., 2006*]. Both diseases are not sex or age dependent, and its pathophysiology remains unclear [*Golovchenko D et al., 2003; Aihara M et al., 2015; Al-Saffar F et al., 2016; Moullan M et al., 2016*]. Predetermination of usage of aromatic antiepileptic antiretroviral sulfanilamide antibiotics and allopurinol is reported for some cases [*Kumar P et al., 2016*]. Historically Stevens-Johnson syndrome and toxic epidermal necrolysis, also recognized as Lyell's syndrome, were categorized as a case of erythema, but nowadays they are referred as different nosologic forms – in case of Stevens-Johnson syndrome affected skin area makes 10% of total skin area and that for Lyell's syndrome is more than 30% [*Łoboda J et al., 2015*]. A number of investigations are concerned with detection and severity evaluation of chronic

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complications in patients suffering from Stevens-Johnson syndrome and toxic epidermal necrolysis [*Chen C et al., 2008; Chang V et al., 2016*].

Modern investigations show diagnostic value of application tests; modern methods of external treatment of allergic complications are studied as well. Authors claim cross disciplinary approach gives a real opportunity for prognosis improvement for the patients with those diseases [*Monov A, 1982; Dityatkovskaya E, 2003; Kaznacheeva L, 2002; Ovchinnikova E et al., 2002; Bolotnaya L, 2005*]. Disease management is mostly based on supporting therapy, though several treatment methods were proposed, such as corticosteroids and intravenous immunoglobulin implementation for course of a disease blocking [*Roujeau J et al., 2011; Sokumbi O, Wetter D, 2012; Sorokina E et al., 2014; Petukhova T et al., 2016; Poletti-Jabbour J et al., 2016*]. It was proposed to implement local or systemic corticosteroids with anti-infective agents to clean lesion skin areas in combination with analgesics, such as diclofenac, because they don't demonstrate side effects when ingested [*Ludwig C et al., 2003; Gregory D, 2016; Teh L et al., 2016*]. Up to date there is no consensus among investigators concerning complex therapy for such patients. Effectiveness of proposed methods remains arguable [*Aihara M et al., 2015*].

We consider important revealing patterns of protein metabolism changes in case of toxico-allergic dermatoses for correct choice of tactics for therapeutic methods. Amino-acid metabolism and amino-acid reserve formation are the main characteristics of metabolism in vivo. Main attention to amino-acid blood composition in clinic practice can be explained by two factors. First, blood amino-acids are metabolically connected, that's why qualitative and quantitative blood amino-acid spectrum can be used as criterion of protein metabolism condition of organism. Second, blood amino-acids are available for investigation and that is a great practical advantage.

Material and methods

The key role of amino-acids in protein and bioactive compound synthesis, their integrative role between metabolic flows defines necessity of free amino-acid reserve study under different pathological conditions, especially for severe toxic allergic dermatosis. The importance of the role of protein metabolism disorder on toxic allergic dermatosis development and course and not sufficient study of peculiarities of amino-acid metabolism and its products for patients with toxic allergic dermatosis and their dependence on clinical implications determined course of our investigations. In order to study different dermatoses the content of amino-acids and their cleavage products was separately evaluated in patients suffering from multiform exudative erythema, Stevens-Johnson syndrome and toxic epidermal necrolysis.

Being the basis of body life, proteins are complex polymers consisting of amino-acids delivered from digestive system as a result of food protein decomposition. Amino-acids play special role in metabolic transformations. Their key role in intermediate metabolism is determined by diversity of the ways and peculiarities of their implementation in complicated systems of regulating mechanisms. Amino-acids are the main elements of protein and bioactive compounds, such as hormones, vitamins, enzymes. They are immune processes regulators and they affect the inner cellular secondary messenger level – Ca^{2+} and phosphoinositide metabolism products [*Eskin O, Zazdravnov A, 1993*].

Amino-acids and their metabolic products in spite of their stimulatory or extinguishing actions on specific receptors can actively take role in antioxidant protection, as well as stabilize oxidation-reduction processes in different tissues.

Pathologic changes and destructive processes development in many cases can be characterized by amino acid misbalance. Amino-acid metabolism distortion can be monitored not only by the level of metabolic products in blood and urine, but by amount of free amino-acids in biological fluids. Amino-acid concentration in blood plasma, as integral value in metabolism, is in the final analysis the characteristic of different processes, such as: exogenous intake of such compounds (nutrient factors), absorption and tissue distribution, redistribution and removal (transportation factor), protein turnovers and intermediate amino-acid exchange, regulated by transamination, decarboxylation, gluconeogenesis and glycolysis reactions (metabolic factor) [*Wright C et al.,1996*].

Table 1

Characterization of amino-acid content (M±m) of blood serum in patients with multiform exudative erythema

Indices	Control group n=20	Patients with multiform exudative erythema n=46
Total amount of amino-acids (*mkMole/l*)	3394.8±107.1	3121.0±84.7
Amount of exchangeable amino-acids (*mkMole/l*)	2134.9±86.1	1887.8±72.6
Amount of non-exchangeable amino-acids (*mkMole/l*)	1071.4±54.7	1022.3±60.1
Amount of partially non-exchangeable amino-acids (*mkMole/l*)	188.5±10.6	210.3±60.1
Amount of sulfur containing amino-acids (*mkMole/l*)	102.4±8.3	68.8±3.2**
Ratio of non-exchangeable to exchangeable amounts of amino-acids	0.50±0.11	0.54±0.08
Ratio of non-exchangeable and partially non-exchangeable to exchangeable amounts	0.59±0.12	0.65±0.10
Methionine to cysteine ratio	0.50±0.10	0.34±0.005*
Asparaginic acid to alanine ratio	0.046±0.011	0.054±0.008
Leucine to isoleucine ratio	1.98±0.12	2.12±0.11
Phenylalanine to tyrosine ratio	1.35±0.19	1.38±0.09
Glutaminic acid to proline ratio	1.06±0.08	0.60±0.05**

Note. *Differences between the indicators of patients and control group individuals are reliable when * - p<0.05; ** - p<0.01*

Results

Content analysis of amino-acid combination in blood serum of patients with multiform exudative erythema revealed a significant decrease of only one total index – amount of sulfur containing amino-acids (p<0.01).

Total amount of amino-acids had no deviation from the norm, amount of exchangeable and non-exchangeable amino-acids decreased, amount of partially non-exchangeable amino-acids increased, but no statistically reliable differences between these indices for healthy people were observed (p>0.05). Ratio of non-exchangeable and partially non-exchangeable amounts to exchangeable amounts of amino-acids showed tendency to increase. Reliable decrease of methionine to cysteine ratio and glutaminic acid to proline ratio was observed (p<0.01). Slight increase leucine to isoleucine ratio, as well as asparaginic acid to alanine ratio has also been observed (p>0.05).

Amino-acid spectrum of blood serum in patients with Stevens-Johnson syndrome was changed as follows: reliable decrease of general amount of amino-acids (p<0.05) due to significant decrease of total amount of exchangeable amino-acids (p<0.05) and non-exchangeable amino-acids (p<0.01), as well as amount of sulfur containing amino-acids (p<0.01). This is accompanied with non-reliable increase of total amount of partially non-exchangeable amino-acids (p>0.05).

In patients of this group ratio of non-exchangeable to exchangeable amounts of amino-acids and ratio of total amount of non-exchangeable and partially non-exchangeable to exchangeable amino-acids remained within norm limits. A significant decrease of methionine to cysteine ratio and increase of asparaginic acid to alanine ratio was observed in patients with Stevens-Johnson syndrome.

Amino-acid reserve study for patients with toxic epidermal necrolysis revealed opposite changes of some indices depending on disease stage.

A significant decrease of total amount of amino-acids due to slight decrease of exchangeable (p>0.05) amino-acids, as well as a significant decrease of non-exchangeable (p<0.01) and partially exchangeable amino-acids was observed. It was accompanied by abrupt decrease of sulfur containing amino-acids (p<0.01). During the second stage of disease (onset of the disease) ratio of non-exchangeable to exchangeable amounts of amino-acids and asparaginic acid to alanine ratio became

Table 2

Characterization of amino-acid content (M±m) of blood serum in patients with Stevens-Johnson syndrome

Indices	Control group n=20	Patients with Stevens-Johnson syndrome n=11
Total amount of amino-acids (*mkMole/l*)	3394,8±107,1	2772,2±86,4*
Amount of exchangeable amino-acids (*mkMole/l*)	2134,9±86,1	1784,6±48,7*
Amount of non-exchangeable amino-acids (*mkMole/l*)	1071,4±54,7	775,5±36,6**
Amount of partially non-exchangeable amino-acids (*mkMole/l*)	188,5±10,6	212,8±14,3*
Amount of sulfur containing amino-acids (*mkMole/l*)	102,4±8,3	67,4±6,9**
Ratio of non-exchangeable to exchangeable amounts of amino-acids	0,50±0,11	0,43±0,10
Ratio of non-exchangeable and partially non-exchangeable to exchangeable amounts	0,59±0,12	0,55±0,14
Methionine to cysteine ratio	0,50±0,10	0,28±0,06*
Asparaginic acid to alanine ratio	0,046±0,011	0,098±0,025*
Leucine to isoleucine ratio	1,98±0,13	2,20±0,17
Phenylalanine to tyrosine ratio	1,34±0,19	1,12±0,13
Glutaminic acid to proline ratio	1,06±0,08	1,03±0,14

Note: *Differences between the indicators of patients and control group individuals are statistically significant significant (* – $p<0.05$, ** – $p<0.01$).*

smaller ($p<0.05$); leucine to isoleucine ratio increased compared to control group. During the height of the disease (third stage) total amount of amino-acids increased the amount of non-exchangeable and sulfur containing amino-acids. Total amount of exchangeable amino-acids showed the tendency to decrease. This was accompanied by ratio increase of non-exchangeable and partially non-exchangeable to exchangeable amounts ($p<0.01$), leucine to isoleucine ratio, and ratio decrease of glutaminic acid to prolin and asparaginic acid to alanine ($p<0.05$).

Discussion

Changes in amino-acid reserve of blood in case of dermatoses (disaminoacidemia in multiform exudative erythema cases, hypoaminoacidemia in Stevens-Johnson syndrome, hypo- and hyperaminoacidemia in different toxic epidermal necrolysis stages) are due to different factors: one is – decrease of amino-acid income from digestive system due to mucosal tunic damage and enzyme production system changes, which leads to distortion of transamination and hydroxylation reactions and correspondingly to liver cell functioning and amino-acid value decrease as a result of axudate formation in inflammation area, the other one – activation of free radical oxidation reactions and so on. But one of the main stimulating factors of amino-acid misbalance of patients is disfunction of neuroendocrinal regulation occurring as a result of immune conflict caused by drug implementation. Let us consider general for all clinical forms and intrinsic for different dermatosis, disorders of amino-acid blood spectrum and figure out their possible causes.

Analysis of the causes of amino-acid spectrum disorders makes us think that disaminoacidemia developing in case of multiform exudative erythema is the result of lypid peroxidation and weakening of antioxidant protection of the organism, that is why amino-acids that take part in the glutathione synthesis in tissues decreased mostly (glycine, cysteine, glutamic acid) and increased value of arginine (nitrous antioxidant) was observed in blood. Changes of the amount of other amino-acids and amines (methionine, proline, ornithine,

Table 3

Characterization of amino-acid content (M±m) of blood serum in patients with toxic epidermal necrolysis

Indices	Control group n=20	Patients with toxic epidermal necrolysis n=13	
		Onset	Height
General amount of amino-acids, *mkMole/l*	3394.8±107.1	2714.29±105.1*	4484.2±183.7**
Amount of exchangeable amino-acids, *mkMole/l*	2134.9±86.1	2001.8±90.7	1848.2±81.6
Amount of nonexchangeable amino-acids, *mkMole/l*	1071.4±54.7	598.4±38.3**	2454.3±101.2**
Amount of partially nonexchangeable amino-acids, *mkMole/l*	188.5±10.6	114.0±9.7*	181.7±12.4
Amount of sulfur containing amino-acids, *mkMole/l*	102.4±8.3	57.5±5.1**	192.3±12.6
Ratio of nonexchangeable to exchangeable amounts of amino-acids	0.50±0.11	0.30±0.08*	1.33±0.17**
Ratio of nonexchangeable and partially nonexchangeable to exchangeable amounts	0.59±0.12	0.36±0.10	1.49±0.19**
Methionine to cysteine ratio	0.046±0.011	0.023±0.006**	0.028±0.008*
Asparaginic acid to alanine ratio	1.98±0.13	2.99±0.31*	1.50±0.22
Leucine to isoleucine ratio	1.34±0.19	1.28±0.19	5.19±0.53*
Phenylalanine to tyrosine ratio	1.06±0.08	0.95±0.10	3.24±0.35*

Note: *Differences between the indicators of patients and control group individuals are statistically significant significant (* – $p<0.05$, ** – $p<0.01$)*

taurine) is connected to them metabolically. Hypoaminoacidemia in Stevens-Johnson syndrome and in the onset of toxic epidermal necrolysis disease can be due to protein synthesis disorder, as well as due to vessel permeability increase and protein exclusion from the vascular bed. Velocity decrease of protein decomposition in amino-acids in oxygen starvation conditions is also possible. Decrease of free amino-acid level in blood in case of Stevens-Johnson syndrome and toxic epidermal necrolysis (onset of the disease) can be possible due to utilization of some of them as energy resources and also as a result of intensive utilization of free amino-acids for rapid protein synthesis evoked by skin lesion. In our point of view the amino-acid value decrease can be treated as result of adaptive mechanism functioning aimed to uphold and increase energetic potential of organism and tissues. Hormonal factors (catecholamines, glucocorticoids, thyroid gland hormones), which surely take part in disease course, also contribute to amino-acid utilization in blood, liver and other organs and tissues.

The increase of free amino-acids in blood of patients with toxic epidermal necrolysis in the height of the disease is due to the action of neurohumoral, hormonal and some other factors, each of them resulting in acceleration of protein breakdown process and release of free amino-acids. That is why free amino-acid increase in blood of patients with toxic epidermal necrolysis directly or indirectly reflects the intensity of tissue protein decomposition (liver, heart, muscles). Free amino-acid accumulation in blood reflects not so much the intensity of protein synthesis or decomposition, but rather the balance between those two processes indicating which process is dominating. It is the prevalence of catabolic processes that causes accumulation of nitrogen in amino-acids in patients with toxic epidermal necrolysis. It can be assumed that the increased protein decomposition is due to function change of adrenal cortex, namely the intensive production of glucocorticoids, and occurs in parallel to the immune conflict. Namely the changes of hormonal profile, due to drug implementation, influence the protein metabolism assuring the predominance of catabolic processes. Tissue decomposition is most likely adaptation reaction, which

results in amino-acid release, necessary for damaged tissue recreation.

Along with the activation of decomposition processes, protein synthesis is most likely disturbed (especially in the height of the toxic epidermal necrolysis disease), and the changes in amino-acid spectrum are aimed to certain homeostasis preservation, compliant to this pathological state. But concentration and proportion disturbances in cell structures are of certain value, because they practically showed that increase of some amino-acids can lead to disappearance of others and whole organism functions' disorder. Loses of exchangeable and non-exchangeable amino-acids, hypoproteinemia, observed in our investigations, decreases organism ability to synthesize proteins in different tissues, creates unfavorable background for tissue regeneration, hampers erosion healing and lowers organism resistivity to infection.

CONCLUSION

Obtained results show that toxico-allergic dermatosis diseases are accompanied by significant changes in the blood parameters of the protein metabolism. Analysis of metabolism intensity and peculiarities revealed features of free amino acid and their metabolic products amount distortion in patients. Degree of disturbances is different in case of multiform exudative erythema, Stevens-Johnson syndrome, toxic epidermal necrolysis diseases due to different necessity of amino-acids in different biochemical processes. It indicates that changes in amino-acid metabolism are important pathogenic section of diseases, defining their severity and prognosis. Knowledge of patterns of protein metabolism changes during toxico-allergic dermatosis is a necessary condition for the correct choice of tactics for therapeutic interventions for the correction of impaired protein metabolism.

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